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Research Article

Enhancing the Therapeutic Efficacy of Daunorubicin and Mitoxantrone with Bavachinin, Candidone, and Tephrosin

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The capability of flavonoids in sensitizing cancer cells was demonstrated in numerous works to chemotherapy and converse multidrug resistance by modulating efflux pumps and apoptosis mechanisms. Three flavonoids, namely, bavachinin, tephrosin, and candidone, have been recently introduced to cancer treatment research presenting various activities, such as antibacterial, immunomodulatory, cell death, and anticancer. Less information exists regarding the therapeutic significance of these flavonoids in cancer treatment, especially in overcoming multidrug resistance (MDR). Here, we tempted to investigate the potency of these agents in reversing MDR by analyzing their effects as chemosensitizers on cell cytotoxicity, P-gp and ABCG2 protein expression levels, and their function on two multidrug-resistant cell lines, P-gp-overexpressing human gastric adenocarcinoma cell line (EPG85.257RDB) and ABCG2-overexpressing human epithelial breast cancer cell line (MCF7/MX). The inhibitory concentration of 10% (IC_{10}) of bavachinin, tephrosin, and candidone in EPG85.257RDB cells was 1588.7 ± 202.2, 264.8 ± 86.15, and 1338.6 ± 114.11 nM, respectively. Moreover, these values in MCF7/MX cell were 2406.4 ± 257.63, 38.8 ± 4.28, and 27.9 ± 5.59 nM, respectively. Expression levels of ABCG2 and P-gp were not significantly downregulated by these flavonoids. Maximum levels of daunorubicin and mitoxantrone accumulations and minimum rates of drug efflux in both cell lines were detected 48 hrs posttreatment with tephrosin and bavachinin, respectively. Chemosensitization to mitoxantrone and daunorubicin treatments was, respectively, achieved in MCF7/MX and EPG85.257RDB cells in response to IC_{10} of bavachinin and tephrosin, independently. These effects did not follow time-dependent manner, and each flavonoid had its cell-dependent patterns. Overall, bavachinin, tephrosin, and candidone showed potency to sensitize MDR cells to daunorubicin and mitoxantrone and could be considered as attractive MDR modulators for cancer treatment. However, their action was time and cell specific.

1. Introduction

A major problem in cancer chemotherapy is drug resistance, not only to single, but to multiple drugs, which significantly compromises treatment outcomes. This phenotype is known as multidrug resistance (MDR), which is characterized by reduced intracellular drug accumulation leading to treatment failure. Variety of factors causes drug resistance; among them, overexpression of ATP-binding cassette (ABC) transporters is the most frequently occurring factor [1, 2]. So far, 49 members of human ABC transporter family have been discovered; among them, P-glycoprotein (P-gp, also referred to ABCB1 or MDR1) and ABCG2 (MXR or BCRP) which are the important members of ABC family attribute to MDR in cancer